

Spontaneous Retro Peritoneal Bleeding with COVID 19: Management Modalities and Mortality Predictors

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Background: COVID-19 infection was associated with high risk of thromboembolism in high-risk patients, so variable anticoagulation agents were used in different doses, as a rare complication of anticoagulants; spontaneous retroperitoneal bleeding (SRB) might occur.

Aim of work: To study SRB associated with COVID-19 infection due to anticoagulation at wider spectrum as regard comorbidities, factors associated with SRB and to discuss available modalities of treatment, factors affecting decision, outcome, and associated mortality with each other.

Methods: 17 patients with COVID-19 presented with SRB, 11 patients were managed surgically, 6 patients were managed conservatively, assessment of comorbidities, timing of intervention and outcome were established.

Results: 6 patients were managed conservatively, 4 of them died due to refractory shock. 11 patients were managed surgically, 8 of them died, 3 out of the 8 deaths were because of Myocardial Infarction, respiratory complications and massive stroke, Timing of surgical consultation was significantly related to management, hemoglobin drop and outcome. Increased blood components need was significantly related to mortality.

Conclusion: Management should be conservative, but with no delay of intervention if needed, this brings better results rather than conservation in progressive hematoma. Vital instability, increased hemoglobin drop and transfusion needs are independent factors that mandate intervention.

Introduction

Since its outbreak, COVID-19 is associated with variable manifestations. Micro thrombosis is considered one of the hallmarks that can lead to pulmonary thromboembolism and then respiratory failure.¹ Cerebral stroke is one of the manifestations of Micro thrombosis.²

Thromboembolic events incidence reaches up to 21% with a mortality rate of ~74% in COVID-19 infected individuals, 11-70% of ICU admitted patients with Covid-19 undergo thromboembolism.³

Although limited evidence multiple studies discussed efficacy of anticoagulation especially in ICU admitted patients with COVID-19 infection and preferred administration of heparin or other substitutes for prophylaxis against thromboembolism.⁴

To our knowledge, this is a rare complication of heparin and there are few reports in the medical literature.⁴

Several randomized controlled trials such as HEP-COVID, IMPROVE-COVID and INHIXACOVID 19 were undertaken to study the efficacy and safety of heparin therapy in patients with severe COVID-19 pneumonia. Recently, there are rising numbers of papers reporting major internal bleeding such as retroperitoneal hemorrhage as a complication of COVID-19 management.^{5,6}

Presence of blood or blood clots in retroperitoneal zone 3 defines pelvic hematoma, which is anteriorly bordered by the urinary bladder dome, posteriorly related to sacrum and iliac wings as lateral borders. SRB secondary to anticoagulant Therapy is one of the well-known but self-limiting

complications. Interestingly, SRB had been reported in a patient with COVID-19 who was not even on anticoagulant therapy and presentation was more severe.⁷

It is debatable to say that bleeding complication is a well-known side effect of anticoagulant because anti-factor Xa testing was not done to support it, and plasma heparin levels are unknown, The cause of bleeding remains unclear.

A prophylactic anticoagulation guideline recommends 40mg of Lovenox once daily for Covid-19 patients with mild symptoms and 0.5 mg/kg of Lovenox twice daily for patients with more severe symptoms or patients that required ICU admission.^{8,9}

Therapeutic anticoagulation is needed in patients with severe respiratory symptoms who need ventilatory support or sharply rising D-dimer.^{8,9}

Delayed treatment and misdiagnosis are two of spontaneous retroperitoneal bleeding (SRB) criteria due to nonspecific clinical manifestations. SRB represents a potentially fatal complication of anticoagulation therapy, with reported incidence and mortality rates of 0.6–6.6% and 10-20%, respectively in general population.¹⁰

When SRB is suspected CT should be the standard imaging procedure. It is useful in evaluation of SRB mass effect by identification of anatomical borders and hematoma location; additionally, bleeding source could be estimated by contrast extravasation.¹⁰

Small cohort studies and single case series give the evidence in management of SRB; however, the summary of treatment

strategy is as "volume support and bleeding stoppage". Medical and conservative management controlled more than 50% of SRB patients by crystalloids, colloids, blood products, inotropic and vasopressor support if needed.^{11,12}

Specific drugs to reverse coagulopathy could be considered when indicated (I.e., vitamin K, protamine sulfate, prothrombin complex concentrates, recombinant factor VIII and IX).¹⁰

Invasive treatment (Interventional radiology procedures and surgery) should be considered if the hemodynamic instability persists with active bleeding sources on CT imaging or in cases of significant abdominal or retroperitoneal compressive symptoms.^{11,12}

Aim of work

Being rare condition and cases in literature are sporadic and rare, and our center is reputable referral center for COVID-19 patients, so we had the chance to managed 17 cases in our center.

1. To study SRB associated with COVID-19 infection due to anticoagulation at wider spectrum as regard comorbidities, factors associated with SRB.
2. To discuss available modalities of treatment, factors affecting decision, outcome, and associated mortality with each other.

Patients and methods

This is a single center study of 17 patients with COVID-19 infection who were associated with spontaneous retroperitoneal bleeding since July 2020 till June 2021, was held in Ainshams University Specialized Hospital in Obour city.

All patients were admitted via transferal from other University hospitals either by being highly suspicious by CT CORADS criteria or by being PCR positive for COVID-19 viral infection.

Patients were under multidisciplinary management from chest, infective diseases and internal medicine physicians as long as they were being ward admitted; anti-microbial treatment involved 10-day oral hydroxychloroquine and lopinavir/ ritonavir, compassionate use of remdesivir for 10 days were administered. Initial empiric ceftriaxone and levofloxacin therapeutic dose of anticoagulation were used, later after multi departmental university meeting, anticoagulation protocol changed to prophylactic doses unless there was associated high risk other than COVID-19 infection, risk factors like atrial fibrillation, history of DVT or cardiac valves surgeries.

On desaturation, vitals instability or any other indication for ICU admission, patient was transferred to ICU for possibility of intubation, BEEP, and inotropic supports administration.

If vital instability occurred, requested imaging study revealed SRB, ICU admission was done for proper strict monitoring.

After surgical consultation we started resuscitation and monitoring for the patient and conservative management was continued under strict monitoring.

Strict vital data monitoring, assessment of abdominal

examination whether generalized or localized peritonism and Urine output monitoring were done.

Pelviabdominal CT (**Fig. 1**) with venous contrast is performed, initial Hemoglobin (HGB) is assessed, sequential follow up for the hematoma size and its complications was done.

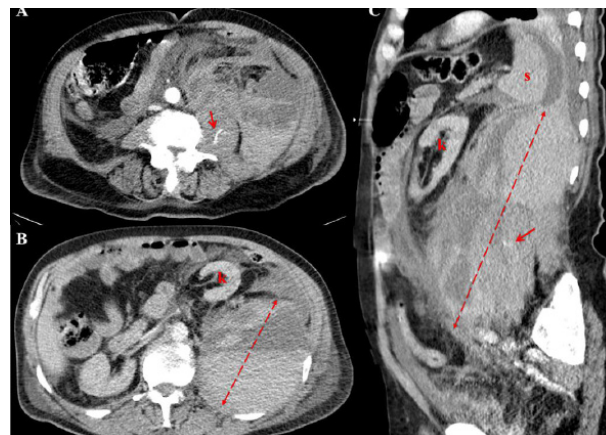


Fig 1: The contrast-enhanced computed tomography scan of the abdomen revealing a large retroperitoneal haematoma involving the left psoas muscle pushing the left colon and the left kidney forward and medially (A-C) with signs of contrast extravasation (arrows, A and C) S, spleen; K, kidney.

Complications might be related to decrease of abdominal compartment like ureteric compression and hydronephrosis, intestinal aperistalsis, deep venous thrombosis of lower limbs.

Complications might be due to resuscitation itself and complications of reversal of anticoagulation like thrombotic complications.

Failure of conservative management mandated surgical intervention, especially if there was no definite bleeding source in CT.

Surgical management (**Figs. 2,3**) primary goals were first to control all active bleeding sources and then to remove the large hematoma. Nevertheless, the removal of the hematoma might increase bleeding by removing its tamponade effect; packing with pads might be the only surgical option. In these cases, the retroperitoneum might need to be packed and re-explored at 24-48 h, only 1 patient didn't undergo packing, 2 patients underwent packing only and 8 patients underwent packing followed by depacking.

6 patients underwent conservative management.



Fig 2: Retroperitoneal hematoma on exploration.

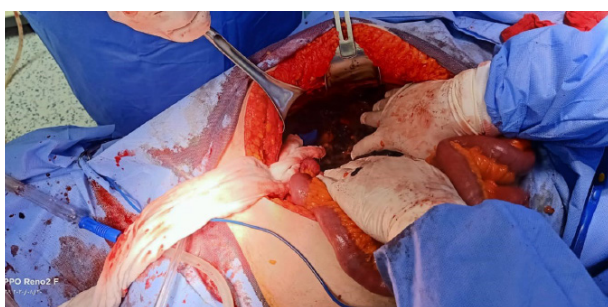


Fig 3: Retroperitoneal hematoma on exploration.

The study is retrospective cohort study

Data registered and collected by specified data collectors.

Results

Following data were collected and interpreted

- **Preoperative data:**

Name, age, gender, comorbidities, initial antiviral treatment, initial anticoagulation, imaging including site and size of hematoma, HGB and HGB drop, initial blood transfusion, initial vital data, interval between consultation and operation.

- **Operative data:**

Cause of intervention, type of procedure

- **Postoperative data:**

Mortality, discharged patients, postoperative complications, thrombotic complications, cause of

death, interval between operation and mortality.

SRB was common in elder population with mean age 60 years old, commonest comorbidity was DM in 82% of patients, all patients had received therapeutic dose of anticoagulation, all patients underwent resuscitation, with failure of conservative management 11 cases were introduced to operative theatre.

Retroperitoneal hematoma was found in different zones (**Table 2**), it was stable in size on follow up in 2 patients, ranging from 6 -20cms, initial HGB drop ranged from 0-7, resuscitation needs started from 2 up to 8 units of packed RBCs.

According to (**Table 3**), Out of 17 patients only 5 survived, 3 of them were surgically managed and 2 managed conservatively, cause of death mainly due to late hypovolemic shock and respiratory and thrombotic complications, bilateral DVT occurred in 1 patient who survived surgical management and that patient underwent IVC filter application.

Interval between admission and surgical consultation was significant (P-value=0.037), this indicates early detection enhances better management initial HGB drop, and blood transfusion were statistically significant that increased HGB drop drove towards surgical management.

Table 5 documents significant difference in management according to vital data, comorbidities. Outcome, complications, mortality and its cause are mentioned but still not significantly different, this may be due to small sample or under estimation.

Increased HGB drop and blood transfusion needs occurred more with mortality, stable hematoma in imaging was significantly related to survival, while hematoma in more than single zone was significantly related to mortality, accidental finding was found in the form that mortality was significantly higher in males.

Again, even whether conservatively or surgically managed didn't affect mortality significantly, also initial size of hematoma even comorbidities statistically didn't affect outcome, type of operation, thrombotic complications occurred didn't provokes mortality significantly although they were fatal except DVT, this might be due to specimen size but could be explained by rarity of the pathology.

Table 1: Initial demographic data and mode of management

		Total no. = 17
Gender	Female	8 (47.1%)
	Male	9 (52.9%)
Age (years)	Mean \pm SD	60.29 \pm 7.51
	Range	50 – 80
Co-morbidities	DM	14 (82.4%)
	HTN	10 (58.8%)
	IHD	2 (11.8%)
Anticoagulation	Clexan	17 (100.0%)
Dose	Therapeutic	17 (100.0%)
Drugs	Solumedrol	16 (94.1%)
	Actemra	8 (47.1%)
	Remdesivir	1 (5.9%)
Interval between admission and consultation (days)	Median (IQR)	2 (1 – 11)
	Range	0 – 13
Management	Operative	11 (64.7%)
	Conservative	6 (35.3%)
Cause of operation	Failed conservative management	11 (100.0%)

Table 2: Clinical and imaging and laboratory data of the patients

		Total no. = 17
Preoperative imaging	Retroperitoneal hematoma	9 (52.9%)
	Pelvic hematoma	4 (23.5%)
	Ant abdominal wall hematoma	2 (11.8%)
	Stable retroperitoneal hematoma	2 (11.8%)
Size (cm)	Median (IQR)	12 (10 – 15)
	Range	6 – 20
Preoperative (initial) blood transfusion	Median (IQR)	4 (4 – 6)
	Range	2 – 8
Initial HGB drop	Median (IQR)	4 (4 – 5)
	Range	0 – 7
Vital data	Unstable	14 (82.4%)
	Stable	3 (17.6%)
Interval between consultation and operation (days)	Median (IQR)	1 (0 – 3)
	Range	0 – 6

Table 3: Outcome of the patients

		Total no. = 17
Outcome	Discharge	5 (29.4%)
	Died	12 (70.6%)
Interval between operation and mortality (days)	Median (IQR)	6 (2 – 6.5)
	Range	1 – 17
Cause of death	Shock (late stage)	7 (58.3%)
	MI	2 (16.7%)
	Stroke	1 (8.3%)
	Respiratory	1 (8.3%)
	MOF	1 (8.3%)
Thrombotic complication	No	13 (76.5%)
	Yes	4 (23.5%)
	MI	2 (11.8%)
	Bilateral DVT	1 (5.9%)
	Stroke	1 (5.9%)

Table 4: Comparison between patients managed conservatively and surgically managed regarding initial data

		Operative	Conservative	Test value	P value	Sig.
		No. = 11	No. = 6			
Interval between admission and consultation (days)	Median (IQR)	10 (2 – 12)	1.5 (1 – 2)	-2.083#	0.037	S
	Range	0 – 13	0 – 2			
Preoperative imaging	Retroperitoneal hematoma	6 (54.5%)	3 (50.0%)	0.234*	0.629	NS
	Pelvic hematoma	3 (27.3%)	1 (16.7%)	0.417*	0.518	NS
	Ant abdominal wall hematoma	2 (18.2%)	0 (0.0%)	1.432*	0.231	NS
	Stable retroperitoneal hematoma	0 (0.0%)	2 (33.3%)	3.536*	0.060	NS
Size (cm)	Median (IQR)	15 (10 – 15)	8.5 (7 – 15)	-1.393#	0.164	NS
	Range	10 – 20	6 – 20			
Preoperative blood transfusion	Median (IQR)	5 (4 – 7)	3 (2 – 4)	-3.068#	0.002	HS
	Range	4 – 8	2 – 4			
Initial HGB drop	Median (IQR)	5 (4 – 6)	2.5 (1 – 4)	-2.615#	0.009	HS
	Range	4 – 7	0 – 5			

P-value > 0.05: Nonsignificant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

*: Chi-square test; #: Mann-Whitney test.

Table 5: Comparison between surgically and conservatively managed patients as regard initial data and outcome

		Operative No. = 11	Conservative No. = 6	Test value	P-value	Sig.
Vital data		11 (100.0%)	3 (50.0%)	6.679*	0.010	S
	Stable	0 (0.0%)	3 (50.0%)			
Outcome	Discharge	3 (27.3%)	2 (33.3%)	0.069*	0.793	NS
	Died	8 (72.7%)	4 (66.7%)			
Co-morbidities	DM	9 (81.8%)	5 (83.3%)	0.006*	0.938	NS
	HTN	6 (54.5%)	4 (66.7%)	0.235*	0.627	NS
	IHD	1 (9.1%)	1 (16.7%)	0.215*	0.643	NS
	Stroke	1 (9.1%)	0 (0.0%)	0.580*	0.446	NS
	HF	2 (18.2%)	0 (0.0%)	1.236*	0.266	NS
	Renal impairment	1 (9.1%)	0 (0.0%)	0.580*	0.446	NS
Cause of death	Shock (late stage)	4 (50.0%)	3 (75.0%)	0.298*	0.585	NS
	MI	1 (12.5%)	1 (25.0%)	0.215*	0.643	NS
	Stroke	1 (12.5%)	0 (0.0%)	0.580*	0.446	NS
	Respiratory	1 (12.5%)	0 (0.0%)	0.580*	0.446	NS
	MOF	1 (12.5%)		0.580*	0.446	NS
Drugs	Solumedrol	10 (90.9%)	6 (100.0%)	0.580*	0.446	NS
	Actemra	4 (36.4%)	Unstable	1.431*	0.232	NS
	Remdesivir	1 (9.1%)	0 (0.0%)	0.580*	0.446	NS
Thrombotic complication	No	8 (72.7%)	5 (83.3%)	0.243*	0.622	NS
	Yes	3 (27.3%)	1 (16.7%)			
	MI	1 (9.1%)	1 (16.7%)	0.215*	0.643	NS
	Bilateral DVT	1 (9.1%)	0 (0.0%)	0.580*	0.446	NS
	Stroke	1 (9.1%)	0 (0.0%)	0.580*	0.446	NS

P-value > 0.05: Nonsignificant; P-value < 0.05: Significant; P-value < 0.01: Highly significant.

*: Chi-square test.

Discussion

Spontaneous intramuscular bleeding in COVID-19 patients was likely to be multifactorial. Such hematomas were known complication of LMWH therapy.² Cough, a common symptom of COVID-19 pneumonia, may increase intra-abdominal pressure, resulting in arterial rupture.³ Invasive ventilation with continuous positive pressure ventilation (CPAP) was also likely to increase intra-abdominal pressure.^{13,14,15}

Javid et al 2021 described a case of psoas muscle hematoma presented with flank pain followed by desaturation and abdominal distention, the case was managed successfully conservatively, and follow up CT 3 months later revealed hematoma absorption.¹⁶

However, conservation might fail, this occurred with Ohn MU et al 2021 who reported a 51-year-old COVID-19 positive woman, prophylactic anticoagulation in the form of intermediate intensity heparin and died from retroperitoneal bleeding.

On day 16 of hospital admission, she had tachycardia and complained of acute abdomen pain. The abdominal examination showed tender and distended abdomen with palpable mass 15×10 cm in the right iliac fossa. Her hemoglobin suddenly dropped 93 g/L with raised lactate of 6.1 mmol/L. Subsequently, CT abdomen was performed, which showed large pelvic hematoma measuring 16×10 cm and compressing the urinary tract system and uterus. The ureter was posteriorly displaced by the hematoma with secondary mild fullness of the right pelvicalyceal system, this patient finally passed away with failure of conservation due to MOF.¹⁷

Table 6: Mortality and survival comparison with different variables

		Discharge	Died	Test value	P-value	Sig.
		No. = 5	No. = 12			
Gender	Female	5 (100.0%)	3 (25.0%)	7.969*	0.005	S
	Male	0 (0.0%)	9 (75.0%)			
Age (years)	Mean ± SD	59.40 ± 6.39	60.67 ± 8.17	-0.308•	0.763	NS
	Range	54 – 70	50 – 80			
Interval between admission and consultation (days)	Median (IQR)	1 (1 – 2)	10 (2 – 12)	-1.759#	0.079	NS
	Range	0 – 3	0 – 13			
Management	Operative	3 (60.0%)	8 (66.7%)	0.069*	0.793	NS
	Conservative	2 (40.0%)	4 (33.3%)			
Preoperative imaging	Retroperitoneal hematoma ^{2,3}	0 (0.0%)	9 (75.0%)	7.969*	0.005	HS
	Pelvic hematoma	2 (40.0%)	2 (16.7%)	0.301	0.301	NS
	Ant abdominal wall hematoma	1 (20.0%)	1 (8.3%)	0.496	0.496	NS
	Stable retroperitoneal hematoma	2 (40.0%)	0 (0.0%)	0.020	0.020	
Size (cm)	Median (IQR)	10 (7 – 15)	13.5 (10 – 15)	-0.595#	0.552	NS
	Range	7 – 20	6 – 20			
Preoperative blood transfusion	Median (IQR)	4 (2 – 4)	5 (4 – 7)	-2.253#	0.024	S
	Range	2 – 4	3 – 8			
Preoperative HGB drop	Median (IQR)	4 (1 – 4)	5 (4 – 6)	-1.774#	0.076	NS
	Range	0 – 5	2 – 7			
Vital data	Unstable	3 (60.0%)	11 (91.7%)	2.435*	0.119	NS
	Stable	2 (40.0%)	1 (8.3%)			
Operation	Packing depacking	3 (100.0%)	5 (62.5%)	1.547*	0.214	NS
	Packing only	0 (0.0%)	2 (25.0%)	0.917*	0.338	NS
	No packing	0 (0.0%)	1 (12.5%)	0.413*	0.520	NS
Co-morbidities	DM	4 (80.0%)	10 (83.3%)	0.027*	0.870	NS
	HTN	4 (80.0%)	6 (50.0%)	1.311*	0.252	NS
	IHD	0 (0.0%)	2 (16.7%)	0.944*	0.331	NS
	Stroke	0 (0.0%)	1 (8.3%)	0.443*	0.506	NS
	HF	0 (0.0%)	2 (16.7%)	0.944*	0.331	NS
	Renal impairment	0 (0.0%)	1 (8.3%)	0.443*	0.506	NS
Thrombotic complication	No	4 (80.0%)	9 (75.0%)	0.049*	0.825	NS
	Yes	1 (20.0%)	3 (25.0%)			
	MI	0 (0.0%)	2 (16.7%)	0.944*	0.331	NS
	Bilateral DVT	1 (20.0%)	0 (0.0%)	2.550*	0.110	NS
	Stroke	0 (0.0%)	1 (8.3%)	0.443*	0.506	NS
Interval between consultation and operation (days)	Median (IQR)	2 (0 – 2)	1 (0.5 – 3)	-0.209#	0.835	NS
	Range	0 – 2	0 – 6			

P-value > 0.05: Nonsignificant; P-value < 0.05: Significant; P-value < 0.01: Highly significant *.

Chi-square test; #: Mann-Whitney test.

Another modality of treatment was discussed by Teta et al for a female 81 years old who complained of pelvic pain, CT shown large hematoma 25 cm with active extravasation from lumbar arteries, selective embolization was done by interventional radiologist, which was successful, patient underwent sudden HGB drop of 6 g/dl few hours later, arrested and died.²⁰

Although this, Gupta et al presented 3 cases were managed successfully by selective embolization for internal iliac, lumbar and obturator arteries and 3 cases discharged in good condition with controlled bleeding.²¹

Successful Surgical intervention could be an option as Conci et al reported 77 years old male presented with severe left upper quadrant abdominal pain with failed conservation, the patient underwent exploration, packing and depacking 48 hours later and discharged after 6 days.

Although first case in literature described in literature was by Scialpi M,²² et al in September 2020 our center registered a case of right upper abdominal quadrant retroperitoneal hemorrhage which was related to IVC and right kidney, unfortunately male 61 years was explored and hematoma was evacuated but he died 2 days later due to MOF, our case was registered in august 2020.

Reversal of anticoagulation associated with thromboembolic complications (Ischemic heart disease, stroke, DVT or pulmonary embolism) could be superadded to morbidity of SRB.

Anticoagulation dosage, although debatable, A retrospective study of 355 patients with COVID-19 done by Musoke et al also convinced that therapeutic anticoagulant was significantly associated with increased risk of bleeding and mortality compared with subtherapeutic (Intermediate dose) or prophylactic dose.¹⁸

In the UK, British Thoracic Society and Scottish Intercollegiate Guidelines Network currently suggested use of prophylactic dose LMWH for patients who were managed on a ward and intermediate-dose LMWH (Twice daily standard prophylactic dose) for patients on critical care and this could be a favorable regimen.¹⁹

Conclusion

Full dose therapeutic anticoagulation for prophylaxis against thromboembolic complications of COVID-19 was associated with risk of fatal retroperitoneal bleeding spontaneously, so prophylactic dose would be preferable and may decrease risk of bleeding.

Management should be conservative, but with no delay of intervention if needed, this brings better results rather than conservation in progressive

hematoma especially in unstable patients with increased hemoglobin drop and transfusion needs.

Although rare, subject is for further multicenter studies for discussion of different treatment modalities of SRB specifically which is associated with COVID-19 infection.

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